UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,937	05/30/2001	Bin Wu	PP-01623.002	8716

7590 12/24/2003

Chiron Corporation
Intellectual Property
P. O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,937	WU ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21 and 23-26* is/are pending in the application.

4a) Of the above claim(s) *6-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,20,21 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed October 6, 2003. Amendments were made to the claims.

Claims 1, 3-21 and 23-26 are pending in the instant application. Claims 6-19 are withdrawn as being drawn to a non-elected invention. Claims 1, 3-5, 20-21 and 23-26 are under consideration in the instant application. Any rejection of record in the previous Office Action, mailed May 6, 2003, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in a previous Office Action, this rejection is made FINAL.

Election/Restrictions

It is noted that Applicant has continued to argue the election/restriction requirement set forth in a previous Office Action. Applicant is reminded that the original arguments set forth in response to the election/restriction requirements have been addressed, and that the election/restriction requirement had been made FINAL. Since Applicant's arguments are merely a reconstruction of those presented in the previous Office Action, the response to the traversal can be found in the previous Office Action.

As it regards the sequences not being chemically distinct, one would not consider the sequence represented as SEQ ID NO: 1 to be prior art for the sequence identified as SEQ ID NO: 3, thus contrary to Applicant's beliefs, these sequences are chemically distinct.

Regarding Applicant's assertion that the Examiner has already searched and considered the multiple sequences (SEQ ID NO: 1, 3 and 5) in the previous Office Action, pointing to

several pages in the Office Action where the sequences are recited, it should be noted that in each of those instances, the Office Action merely states that these sequences are *disclosed in the specification*, and does not in any way indicate that any search or consideration has been made with respect to SEQ ID NO: 3 and 5. In fact, contrary to Applicant's assertion, the previous Office Action clearly states on page 2, third paragraph, that *only* SEQ ID NO: 1 will be searched. Therefore, there is no evidence that any other sequence has been searched or considered.

Information Disclosure Statement

The information disclosure statement filed October 6, 2003 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 20-21 and 23-26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Claims 1, 3-5, 20-21 and 23-26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed October 6, 2003 have been fully considered but they are not persuasive. The following argument was presented in response to the Written Description rejection:

Applicant has provided an adequate written description of all of the possible antisense oligonucleotides to SEQ ID NO: 9 simply by providing the sequence of SEQ ID NO: 9. The premise of the argument is that the skilled artisan would be able to construct any nucleotide sequence that would specifically hybridize to SEQ ID NO: 9 by simply making a complementary sequence (see page 6, paragraphs 4 and 5 of Applicant's arguments).

Applicant's argument is not convincing for the following reason:

The Written Description of an antisense molecule goes far beyond simply designing a molecule that is complementary to the sequence of interest, in the instant case SEQ ID NO: 9. Designing an antisense molecule requires that the molecule have a specific function; i.e., the molecule must be able to hybridize to the target nucleic acid *and* inhibit its expression. Thus, in order to describe an antisense molecule, there must be a description of a structure-function relationship between the antisense molecule and its target gene. There is nothing in the instant

specification or in the present arguments that indicates a structure-function relationship. The assertion that any complementary nucleotide can serve as an antisense molecule is erroneous, and this is adequately established in the rejection set forth in the previous Office Action. Specifically, the examiner cites Branch (*TIBS* **23**: 45-50, 1998), which establishes that not all complementary nucleotides can serve as antisense molecules. In particular, Branch establishes that there are many considerations to be made when designing a functional antisense molecule, such as the exposed regions of the target nucleic acids (due to the unpredictable secondary structures of the target mRNA) and the non-antisense effects of a complimentary molecule, which are prevalent in the technology (again, see p. 45-46 of Branch). The instant specification does not establish what 17 or 25 nucleotides (as recited in the amended claims) will meet these functional limitations, thus there is no description of a structure-function relationship. The fact that one can randomly choose complimentary polynucleotides to hybridize to a particular target sequence does not allow them to envision which of these molecules will exhibit an antisense function.

In conclusion, the Office has met the burden by which to question the Written Description of the instantly claimed invention, setting forth the pitfalls of presuming a molecule has antisense activity simply because it is complimentary to a target mRNA. This is clear by the recitation of the Branch reference on pages 5-6 of the Non-Final Office Action mailed May 6, 2003. Applicant has not refuted the veracity of the reference, or shown how the teachings of the instant specification overcome the pitfalls set forth in the Branch reference. As a result, the Written Description of any KIAA0175 antisense molecule has not been established, and the rejection is maintained.

Applicant's arguments filed October 6, 2003 have been fully considered but they are not persuasive. The following arguments were presented in response to the Enablement rejection:

1. With regard to the Quantity of Experimentation required to practice the invention, Applicant asserts that the instant specification establishes methods of testing an oligonucleotide for antisense activity (see page 8, first and second paragraphs of Applicant's arguments). The skilled artisan would be able to employ any such method to identify an antisense oligonucleotide.

2. With regard to the Amount of Guidance/Working Examples, Applicant asserts that the instant specification provides clear directions toward performing the experimentation required to identify KIAA0175 antisense molecules (see page 9, first full paragraph of Applicant's arguments). Furthermore, Applicant asserts that an example is provided on pages 39-40 showing the operative use of KIAA0175 antisense oligonucleotides to inhibit KIAA0175 expression, thereby providing a working example that is applicable to all KIAA0175 antisense molecules (see page 9, second full paragraph of Applicant's arguments).

3. With regard to the Nature of the Invention, Applicant asserts that the invention has been inappropriately ascribed a gene therapy function, and strenuously asserts that the invention has a much broader nature than gene therapy. Applicant asserts (in their arguments) that, "the invention could be used to test the effects of radiation and chemotherapeutic agents effects on cells, in vitro" (see page 10, second full paragraph of Applicant's arguments).

4. With regard to the State of the Art, Applicant asserts that the invention is not drawn to antisense technology and procedures generally; instead the invention (i.e., the new information brought to the field) is directed to the identity of the gene (see for example page 11, second full

paragraph of Applicant's arguments). It is again asserted that gene therapy is not the focus of the invention.

5. With regard to the Relative Skill in the Art, Applicant asserts that it would not defeat the enablement of the invention if the skilled artisan was required to learn and become proficient in techniques required to practice the art, and it is not the responsibility of the inventors to overcome the deficiencies of the art (purported to be gene therapy) in order to enable the invention (see page 12, first full paragraph of Applicant's arguments).

6. With regard to the Unpredictability of the Art, Applicant simply asserts that one of skill in the art would predict that any antisense molecule directed to KIAA0175 would inhibit the expression of KIAA1075 mRNA. Furthermore, Applicant is under the impression that the transfection step of an antisense molecule is the only area of unpredictability associated with the instant invention (see page 12, second and third full paragraphs of Applicant's arguments).

7. With regard to the Breadth of the Claims, Applicant argues that the skilled artisan could routinely identify or construct a KIAA0175 antisense nucleic acid.

Applicant's arguments are not persuasive for the following reasons:

1. The ability to identify an antisense molecule is not commensurate with the ability to make and use an antisense molecule, contrary to Applicant's assertion. While there may be ways to test the ability of a polynucleotide to serve as an antisense molecule, this does not allow the skilled artisan to make such a molecule without undue and unpredictable trial and error experimentation. In fact, Applicant's assertion that these molecules can be discovered implicitly states that they have not been made, but are instead subject to empirical experimentation. In other words, the skilled artisan cannot look at the specification and make just any functional antisense molecule

because the skilled artisan must identify this molecule since it is not taught in the specification. Considering the unpredictable nature of antisense technology (addressed in detail in section 6 below), this experimentation is necessarily undue and unpredictable trial and error experimentation. In effect, the assertion that the skilled artisan can perform experiments to find the claimed molecules is an invitation to experiment.

2. First, the guidance provided in terms of teaching the experiments to be performed for the identification of KIAA0175 antisense molecules is insufficient because, as set forth above in section 1, identifying a molecule is not commensurate with the ability to make and use the antisense molecule. Second, regarding Applicant's assertion that pages 39-40 display working examples of KIAA0175 antisense molecules, it is noted that these examples do not test the relevant nature of the invention, which is gene therapy (the accuracy of this determination is addressed below in section 3). Additionally, the few examples indicated do not establish a structure-function relationship that is commensurate with the broad scope of the claimed invention, that being any KIAA0175 antisense molecule (the breadth of the claims is discussed further in section 7 below), even if they were performed in a relevant system. That being said, the skilled artisan would not be able to make and use the claimed invention (i.e., the use of any KIAA0175 antisense molecule for therapeutic purposes) commensurate with the scope of the claims.

3. The assertion that the invention is not directed to therapeutic purposes is unclear, especially in light of the instant specification which states on page 1, lines 13-14, "Such compositions and methods are useful as chemotherapy and radiation sensitizers, and as a consequence, find utility in the treatment of neoplastic disease." Thus, the use of these molecules for therapeutic purposes

(in other words, antisense gene therapy) is clearly set forth as the utility of the claimed invention. Furthermore, the assertion that the compositions can be used to test the effectiveness radiation and chemotherapeutic agents for their effect on cells, *in vitro*, is not set forth in the specification anywhere (nor is it pointed to by applicant in their arguments); therefore, upon reading the specification, the skilled artisan would clearly interpret the compositions were to be used for gene therapy purposes, and not to test the effectiveness of radiation and chemotherapy agents *in vitro*. Furthermore, even if the use of the claimed invention to test the effectiveness radiation and chemotherapeutic agents for their effect on cells, *in vitro*, this simply lends itself to the use of the antisense compositions as antisense gene therapy agents, *in vivo*, to sensitize cells for radiation and chemotherapy, as the results of the *in vitro* tests would only be relevant in situations where cells are inhibited for KIAA0175 expression. Thus, the interpretation of the Nature of the Invention is properly made as a composition for use in antisense gene therapy purposes, which therefore requires that antisense gene therapy must be enabled.

In addition, although many of the references set forth in the Office Action address gene therapy considerations for antisense technology, it is not simply the gene therapy aspect of the field that makes the invention unpredictable. Rather, it is the basic scientific principles that are the root of the problem with antisense gene therapy that apply to the instant invention. The Office Action has provided several references (Branch, Jen *et al.*) that clearly establish the basic scientific principles that are problematic when dealing with antisense technology. These principles, the inability to predict the secondary structure of an mRNA, which leads to the inability to accurately make a functional antisense molecule that will bind to and inhibit the expression of a gene from an mRNA, as well as the non-antisense effects of nucleotide

sequences, persist even in the absence of a gene therapy use for the invention. The skilled artisan would be unable to make these functional nucleotides for purposes outside of gene therapy, including the purported use *in vitro* to identify or characterize radiation and chemotherapeutic agents. Applicant's arguments fail to address the veracity of any of these documents, and also fail to establish how the instant specification overcomes the deficiencies set forth by the references, which would be necessary in order for the skilled artisan to make and use the invention.

4. Applicant's assertion that the filed of the invention is not drawn to antisense technology is erroneous, as evidenced by the fact that the claims are drawn to *antisense molecules*. If the field of the invention were the sequence of the gene, then the claims would read on the sequence of the gene as opposed to an antisense sequence to this gene. Thus, the field of the invention must be antisense technology. As set forth above in section 3, Applicant has failed to address any of the references establishing the unpredictable nature of antisense technology, both as it applies to gene therapy, and in terms of the underlying scientific principles leading to the deficiencies in the use of antisense molecules for therapeutic purposes. Therefore, the references are still found to apply with respect to establishing the State of the Art as it relates to the instant invention.

5. Applicant's assertion that the instant specification does not need to overcome the deficiencies of the state of the art is untrue. In fact, this is the root of the enablement rejection: The skilled artisan must be able to make and use the invention; if the state of the art teaches that the invention is unpredictable, then the instant specification must overcome the deficiencies in order for the skilled artisan to make and use the invention. Otherwise, the skilled artisan is left to perform undue and unpredictable trail and error experimentation in an empirical fashion to

overcome the deficiencies of both the state f the art and the instant specification. In the instant case, the Office has established that deficiencies exist in the field of antisense technology, particularly as it relates to gene therapy, by supplying references stating these problems. As set forth above in section 3, Applicant's arguments have both failed to address the veracity of these references and failed to show how the instant specification overcomes the deficiencies set forth by the references.

6. Applicant simply offers an opinion that the skilled artisan would be able to reasonably predict that any nucleic acid complimentary to KIAA0175 would serve as an antisense molecule, without providing evidence to that assertion. In contrast, the Office has supplied several references that discuss the underlying basic principles that lead to the unpredictable nature of antisense technology (e.g., the inability to predict which oligonucleotides will actually bind to an mRNA, let alone inhibit its expression, especially in light of the unpredictable nature of mRNA secondary structure formation). Applicant does not refute these references, and there is no indication of how the instant specification overcomes these deficiencies. In the absence of such evidence, the argument that the invention is simply predictable carries no weight, especially in light of the references supplied by the Office.

7. Applicant again argues that the skilled artisan could identify an antisense molecule to KIAA0175, given the teachings of the instant specification. Applicant is reminded that the claimed invention is not a method of identifying antisense nucleic acids. Rather, the invention is drawn to the actual nucleic acids that can supposedly be identified. Thus, the skilled artisan must be able to make and use these nucleic acids, which cannot be done if these nucleic acids are not already identified/known (i.e., how can one make something if it does not know what it looks

like in terms of a structure-function relationship). Furthermore, as set forth above in section 1, the ability to identify something is not the standard required to meet the Enablement requirement; that standard is the ability to make and use the claimed invention, which is not commensurate with the ability to identify.

In conclusion, the previous Office Action clearly establishes a prima facie case for lack of enablement as it regards the instantly claimed invention by submitting scientific arguments and supporting references indicating the unpredictable nature of the antisense art. In response, Applicant has asserted that the invention is not directed to methods of gene therapy, yet this is the asserted utility in the specification, and there is no indicated support in the specification for an alternative utility. Applicant further asserts that the specification clearly teaches how to identify the claimed antisense molecules, yet this does not teach how to make the claimed molecules. The State of the Art clearly indicates the unpredictable nature of antisense molecules, in the context of basic scientific principles and in the context of gene therapy, which is not overcome by the instant specification. Applicant fails to recognize and address the references cited by the Office that establish the unpredictability of the claimed invention. The reliance on the ability to identify the claimed antisense molecules is not the standard for enabling an invention, and is merely an invitation to experimentation. This experimentation is clearly of an undue and unpredictable nature due to the deficiencies of the antisense art. Therefore, it is only possible to maintain the enablement rejection set forth in the previous Office Action due to a lack of evidence establishing that the claimed invention is enabled.

Allowable Subject Matter

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER